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09/863,803	05/22/2001	Jeffrey J. Rade	71699/55591	8907

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EXAMINER	
LI, QIAN J	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/14/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/863,803	Applicant(s) RADE ET AL.	
	Examiner Janice Li	Art Unit 1632	

-- The MAILING DATE of this communication appears on th cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4 & 5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

Claims 1-28 are pending and under current examination.

Priority

This application claims the benefit of priority from the U.S. provisional application, 60/206,162, filed 05/22/2000.

Claim Objections

Claim 7 is objected to because the word "claim" is missing before "6" in line 1. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the

application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings, or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

The claims 1 and 24 are directed to a method for treating vascular graft, comprising introducing into susceptible cells of a vascular graft an effective amount of at least one nucleic acid encoding *one agent that increases activated protein C* (APC) in the graft. Claim 28 is directed to a kit comprising such agents. Given the broadest reasonable interpretation, the term "*one agent that increases activated protein C*" encompasses numerous (a genus of) agents, which are functionally capable of increasing activated protein C in a vascular graft, which are essential for realization of the claimed method. However, the specification fails to provide an adequate disclosure for the genus of the claimed invention in terms of distinguishing characteristics of the genus.

The specification discloses "*Particular APC enhancing agents according to the invention include TM as well as functional fragments thereof, as well as other agents that increase APC substantially independently of the TM", "Examples of such agents ...include identified endothelial cell protein C receptor (EPCR)*" (last paragraph on page

7). In view of the art known activating proteins for protein C, *Eible et al* (US 5,571,786) teach that the only known activator is thrombin-thrombomodulin complex (column 1, lines 18-29). *Fukudome et al* (US 6,399,064) teach that protein C may both control coagulation and influence inflammation, that molecular basis for regulation of protein C pathway components have yet to be elucidated (column 1). Therefore, it is unclear, aside from the TM, what other agents could increase the APC levels. Considering the numbers of known or unknown agents that could potentially increase the levels of the APC, the disclosed TM and EPCR are not the representative species of the genus. Therefore, the specification fails to provide an adequate description to teach the structures, the identifying characteristics, and the structure-function relationship of the genus of agents that are capable of enhancing the APC, and accordingly does not provide a reasonable guide for those seeking to practice the invention.

An adequate written description for a nucleic acid molecule or active agents requires more than a mere statement that it is part of the invention; what is required is a description of the chemical structures and physical properties of the molecule itself. It is not sufficient to define the molecules solely by its principal biological property, i.e. "increases activated protein C in the graft", because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any molecule with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all molecules that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to

preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). With respect to the method claims, adequate description of the methods first requires an adequate description of the materials used in the method, which provide the means for practicing the invention. The court has made it very clear "CONCEPTION OF CHEMICAL COMPOUND REQUIRES THAT INVENTOR BE ABLE TO DEFINE COMPOUND SO AS TO DISTINGUISH IT FROM OTHER MATERIALS, AND TO DESCRIBE HOW TO OBTAIN IT, RATHER THAN SIMPLY DEFINING IT SOLELY BY ITS PRINCIPAL BIOLOGICAL ACTIVITY". *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of *APC enhancing agents*. Therefore, only the described thrombomodulin and EPCR meet the written description provision of 35 U.S.C. §112, first paragraph.

Claims 1-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for introducing a nucleic acid encoding thrombomodulin to cells of vascular graft *ex vivo* or via routes of direct delivery to the graft *in vivo*, and expressing such in the vascular graft, does not reasonably provide enablement for introducing a nucleic acid encoding any agent that increases the APC by *any* route of delivery to the graft, and it does not reasonably provide enablement for

engineering a vascular graft that *resists failure*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the nature and scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention without undue experimentation.

Claim 24 recites, "a method for engineering a vascular graft that *resists failure*". Although claim 1 does not require a particular therapeutic use, in view of the specification, the claims clearly or implicitly state the intended use of the composition and methods. With respect to claim breadth, the standard under 35 U.S.C. §112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. "WHEN A COMPOUND OR COMPOSITION CLAIM IS LIMITED BY A PARTICULAR USE, ENABLEMENT OF THAT CLAIM SHOULD BE EVALUATED BASED ON THAT USE". (MPEP 2164.01c) When analyzing the enabled scope of the claims, the intended use is to be taken into account because the claims are to be given their broadest reasonable interpretation that

is consistent with the specification. "a graft that resist failure" is defined as a composition for therapeutic use, to prevent, alleviate, and treat the vascular graft failure in the host, therefore, will be evaluated by the standard. As such, the broadest reasonable interpretation of the claimed invention properly encompasses gene therapy for vascular graft failure, particularly those caused by neointimal formation and graft closure, therefore, the claims will be evaluated by that standard.

The specification teaches that using *ex vivo* approach, a replication defective adenoviral vector encoding TM was introduced to vascular grafts, and the TM was expressed *in vivo* for up to 42 days after implantation, that such procedure reduced bound thrombin activity, and increased the ability for endothelial cells to generate APC (example 5 and fig. 10). The specification speculates that "*protein C is activated to APC thereby inhibiting local thrombin generation. Such local and especially robust inhibition of thrombin generation reduces or eliminated thrombus formation in subject vascular grafts*". (last paragraph in page 6). However, the specification is silent regarding whether the increased graft APC has translated to clinical benefit, e.g. an increased graft survival rate or resistant to graft closure. The specification fails to provide an enabling disclosure commensurate with the scope of the claims.

In view of the state of the art and levels of the skilled in the relevant art, it is known that TM plays a critical role in thrombosis, thus is important in preventing and alleviating the vascular graft failure, *French et al* (US 6,290,949) contemplated to transduce grafts of vascular vein or arteries with a nucleic acid encoding TM and/or protein C in combination with conventional pharmaceutical reagents to prevent

accelerated atherosclerosis and restenosis which confounds autologous vascular graft transplantations (see particularly columns 16-18). However, the result of such manipulation is unknown prior to the filing of the instant application. Contrary to the predicted effect, several post-filing arts teach that the graft survival does not correlate well with the levels of TM. *Quyang et al* evaluated 79 women with or without SVG, and found that TM do not correlate with early SVG failure in these population (Circulation 2001 Oct;104:17S,pp.II.406). *Kim et al* (Circ Res 2002 ;90 :205-12) also teach that increased levels of TM and APC in Adv-TM transfected vascular graft did not result in the reduction in neointimal formation. In view of such, the invention does not appear to be enabled absence of clarification of the contradictory evidence found in the references.

Claims 6-12 recite that the Adv-TM transduced graft comprises sufficient APC to prevent or treat early or late graft failure and to exhibit at least about 10% decrease in accelerated atherosclerosis, however, the specification fails to disclose that the method could achieve such outcome.

The claims further embrace any type of introduction of nucleic acids including systemic delivery, which requires targeting the nucleic acid to the selected site of graft, however, the specification fails to provide an enabling disclosure to support the full scope of the claims. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, *Miller* (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in*

vivo gene therapy, and conclude that "FOR THE LONG-TERM SUCCESS AS WELL AS THE WIDESPREAD APPLICABILITY OF HUMAN GENE THERAPY, THERE WILL HAVE TO BE ADVANCES...TARGETING STRATEGIES OUTLINED IN THIS REVIEW, WHICH ARE CURRENTLY ONLY AT THE EXPERIMENTAL LEVEL, WILL HAVE TO BE TRANSLATED INTO COMPONENTS OF SAFE AND HIGHLY EFFICIENT DELIVERY SYSTEMS" (page 198, column 1). *Deonarain* (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy is the "ABILITY TO TARGET A GENE TO A SIGNIFICANT POPULATION OF CELLS AND EXPRESS IT AT ADEQUATE LEVELS FOR A LONG ENOUGH PERIOD OF TIME" (page 53, first paragraph). With regard to the particulars of vascular gene therapy, *Andrew et al* (Curr Opin Cardiol 1999;14:489-494) teach, "SUCCESSFUL GENE THERAPY DEPENDS ON BRINGING TOGETHER IN A CONVENIENT EXPERIMENTAL SETTING (OR IN THE CLINIC) FOUR KEY FACTORS: AN APPROPRIATE STRATEGY FOR GENETIC MANIPULATION, A SUITABLE TARGET GENE, AN EFFICIENT DELIVERY METHOD, AND AN EFFECTIVE VECTOR", in view of these factors, "VEIN GRAFT ATHEROMA REMAINS A CHALLENGE FOR THE FUTURE" (see particularly abstract and introduction). A systemic vector delivery in vascular gene therapy requires to access the lesion and occlude the vessel for an adequate amount of time to allow vector attachment and uptake without significantly compromising myocardial perfusion, thus, the art-known practice has been focused on the local delivery. The specification fails to teach how to overcome the art known difficulties to achieve efficient systemic delivery, therefore, fails to provide sufficient guidance for the skilled artisan to practice the invention without first carrying out undue experimentation.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for obtaining a transduced vascular graft that resists graft failure, in

particular for using numerous agents that increase APC via any routes of vector delivery, the lack of direction or guidance provided by the specification, and the breadth of the claims directed to a decreased atherosclerosis, it would have required undue experimentation for one skilled in the art to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite because of the claim recitation, "susceptible cells", the specification does not define the meaning of the term, and it is unclear what kind of cells the claims embrace.

The following art rejections applied even though the Examiner is aware of the contradiction in the sections of enablement rejection and art rejection. However, in view of the Office policy for compact prosecution, all issues relevant will put forward in the first action on merits.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-6, 8-22, and 24-27 are rejected under 35 U.S.C. 102(e) as being anticipated by *French et al* (US 6,290,949).

The claims are directed to a method for treating vascular graft, comprising introducing into susceptible cells of a vascular graft an effective amount of at least one nucleic acid encoding one agent that increases activated protein C (APC) in the graft, expressing the agent so that APC is increased in the graft for at least about a week; wherein the introduction of the nucleic acid is performed in vivo or ex vivo and then transplanted to a host, wherein the agent is human thrombomodulin (TM) or a functional fragment thereof, and preferably in combination with other anticoagulant molecule, wherein the nucleic acid is inserted into a cassette that includes a promoter and sitting in a vector, wherein the vector comprises sequences from adenovirus, preferably a replication defective adv, wherein the host is susceptible to an inflammatory stimulus and the method further comprising administering a therapeutic amount of at least one-anti-coagulant, anti-thrombotic drug to treat or prevent the stimulus. Claims 25-27 are

drawn to engineered vascular graft, preferably an autologous saphenous vein graft (SVG), or an arterial graft.

French et al teach a method for delivering vectors carrying therapeutic agents to cardiovascular cells such as the smooth muscle cell or endothelial cell in a host suffering vascular injury or immunological rejection of transplanted organ and tissues (column 5, lines 24-30), or underwent angioplasty (column 6, line 67), wherein the vector comprises coding sequences for thrombin inhibitors such as TM, and the protein C, etc. (column 5, lines 39-42), wherein the vector could be introduced into the cells of autologous SVG or arteries by in vivo or ex vivo routes (see columns 17-18). *French et al* go on to teach that two or more different therapeutic gene sequences can be provided (column 16, lines 44-67), the transgene expression could last for weeks, and the vector could be used in combination with conventional drugs, such as anti-thrombin factors (column 17, lines 15-30). *French et al* also teach expression cassette having a promoter (column 12, lines 15-17) and replication defective Adv (column 14, lines 43-44). Therefore, the teachings of *French et al* anticipate the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6, and 8-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over *French et al* (US 6,290,949) as applied to claims 1-6, 8-22, and 24-27 above, and in view of *Larson et al* (US 6,309,380).

Claim 23 is directed to an anti-coagulant drug, coumadin. Claim 28 is directed to a kit comprising one or more of the agents for increasing the APC, means for detecting cell expression of the agents, and APC levels in the blood, and directions for using the kit. *French et al* teach using a delivery vector in combination with an anti-coagulant agent (column 17, lines 15-30), but do not particularly recite "coumadin". *French et al* also teach various factors that could be expressed by the vectors and increase levels of the APC, such as TM and protein C (column 5, lines 40-59), but do not particularly recite a kit.

Larson et al teach conventional anti-coagulants known in the art, such as coumadin (see paragraph bridging columns 1 & 2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to select one of the conventional anti-coagulant drugs taught by *Larson et al* in the methods taught by *French et al* with a reasonable expectation of success. It would also have been obvious to one of ordinary skill in the art at the time the invention was made to present the recited agents as a kit in a commercial process for the convenience and profit of the commercial activity. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 9:00 am - 5:30 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
August 5, 2002

JAMES KETTER
PRIMARY EXAMINER